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This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

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INVENTOR(s) / APPLICANT(s) Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
LUO	Zhiyong		San Diego, California
WILLIAMS	John	P.	San Diego, California
TELLEW	John	E.	Jolla, California

TITLE OF THE INVENTION (280 characters max)

CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

Correspondence Address:

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5929
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-0939	Country	United States of America

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Respectfully submitted,
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Registration No.: 43,708

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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PI60641P

CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

FIELD OF THE INVENTION

This invention relates generally to CRF receptor antagonists and to methods of treating disorders by administration of such antagonists to a warm-blooded animal in need thereof.

BACKGROUND OF THE INVENTION

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide (Vale et al., *Science 213*:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA 80*:4851, 1983; Shibahara et al., *EMBO J. 2*:775, 1983).

CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science 213*:1394-1397, 1981). Briefly, CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science 224*:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol. 124*:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm. 110*:602-608, 1983), adrenals (Udelsman et al., *Nature 319*:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology 122*:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology 118*:1171-1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology 113*:657-662, 1983). The receptor for CRF has now been cloned from rat (Perrin et al., *Endo 133*(6):3058-3061, 1993), and human brain (Chen et al., *PNAS 90*(19):8967-8971, 1993; Vita et al., *FEBS 335*(1):1-5, 1993). This receptor is a 415 amino acid protein comprising seven membrane spanning domains. A comparison of identity between rat and human sequences shows a high degree of homology (97%) at the amino acid level.

In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine, autonomic, and

behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest. 90*:2555-2564, 1992; Sapolsky et al., *Science 238*:522-524, 1987; Tilders et al., *Regul. Peptides 5*:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature 297*:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res. 278*:332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology 110*:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology 110*:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences 30*:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol. 253*:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology 22*:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature 305*:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol. 255*:R744, 1988). Furthermore, clinical data suggests that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem. 25*:215-223, 1990). Accordingly, clinical data suggests that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

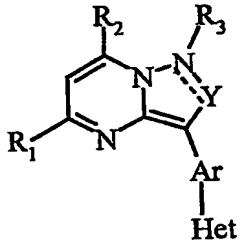
The first CRF receptor antagonists were peptides (*see, e.g.*, Rivier et al., U.S. Patent No. 4,605,642; Rivier et al., *Science 224*:889, 1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. More recently, small molecule CRF receptor antagonists have been reported Published patent documents include US6313124, WO 01/23388, and WO 97/29109, all of which disclose pyrazolopyrimidine compounds as CRF antagonists. Published application WO 98/54093 describes certain pyrazolopyrimidine compounds as tyrosine kinase inhibitors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurological conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists, and more specifically to CRF receptor antagonists having the following general structure (I):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R_1, R_2, R_3, Y, Ar, and Het are as defined below.

The CRF receptor antagonists of this invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of disorders or illnesses, including stress-related disorders. Such methods include administering an effective amount of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition, to an animal in need thereof. Accordingly, in another embodiment, pharmaceutical compositions are disclosed containing one or more CRF receptor antagonists of this invention in combination with a pharmaceutically acceptable carrier and/or diluent.

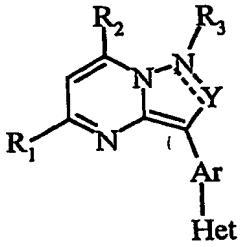
These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are

set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compounds useful as corticotropin-releasing factor (CRF) receptor antagonists.

In a first embodiment, the CRF receptor antagonists of this invention have the following structure (I):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof,

wherein:

"---" represents the second bond of an optional double bond;

R_1 is hydrogen, alkyl, substituted alkyl, $-NH_2$, or halogen;

R_2 is $-NR_7R_8$ or $-OR_{10}$;

R_3 is null, hydrogen, or alkyl;

Y is $=(CR_4)-$ or $-(C=O)-$;

R_4 is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl optionally substituted with 1 or 2 R_5;

R_5 at each occurrence is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfinyl, or alkylsulfonyl;

Het is heteroaryl optionally substituted with 1 or 2 R_6;

R_6 at each occurrence is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, or hydroxy;

R_7 is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, or alkoxyalkyl;

R_8 is alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, alkoxyalkyl, substituted alkoxyalkyl, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, arylalkyl, or substituted arylalkyl; or

R_7 and R_8, together with the nitrogen atom to which they are attached, form a heterocycle which is optionally substituted by 1, 2, or 3 R_9;

R_9 at each occurrence is hydrogen, hydroxy, alkylsulfonyl, alkylsulfinyl, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, alkoxyalkyl, or substituted alkoxyalkyl; and

R_{10} is alkyl, substituted alkyl, heteroarylalkyl, substituted heteroarylalkyl, aryloxyalkyl, or substituted aryloxyalkyl.

As used herein, the above terms have the following meaning:

"Alkyl" means a straight chain or branched, noncyclic or cyclic, unsaturated or saturated aliphatic hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -CH_2-cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls, also referred to as "homocyclic rings," and include di- and poly-homocyclic rings such as decalin and adamantyl. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Alkylidenyl" represents a divalent alkyl from which two hydrogen atoms are taken from the same carbon atom, such as =CH_2, =$CHCH_3$, =$CHCH_2CH_3$, =$C(CH_3)CH_2CH_3$, and the like.

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atoms replaced with an aryl moiety, such as benzyl (*i.e.*, -CH_2phenyl), -CH_2-(1 or 2-naphthyl), -$(CH_2)_2$phenyl, -$(CH_2)_3$phenyl, -$CH(phenyl)_2$, and the like.

"Aryloxyalkyl" means an aryl attached through an oxygen bridge to an alkyl (*i.e.*, aryl-O-alkyl-) such as -methyl-O-phenyl, and such.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10-members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as -CH_2-pyridinyl, -CH_2-pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocycle ring") means a 5- to 7-membered monocyclic, or 7- to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocycle rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2morpholinyl, and the like.

The term "substituted" as used herein means any of the above groups (*i.e.*, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("-C(=O)-") two hydrogen atoms are replaced. "Substituents" within the context of this invention include halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,

heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aR_b$, $-NR_aC(=O)OR_b$ $-NR_aSO_2R_b$, $-OR_a$, $-C(=O)R_a$ $-C(=O)OR_a$, $-C(=O)NR_aR_b$, $-OC(=O)NR_aR_b$, $-SH$, $-SR_a$, $-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$, $-S(=O)_2OR_a$, wherein R_a and R_b are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo and iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like. Haloalkyl is a specific embodiment of substituted alkyl, wherein alkyl is substituted with one or more halogen atoms.

"Alkoxy" means an alkyl moiety attached through an oxygen bridge (*i.e.*, -O-alkyl) such as –O-methyl, -O-ethyl, and the like.

"Thioalkyl" means an alkyl moiety attached through a sulfur bridge (*i.e.*, -S-alkyl) such as –S-methyl, -S-ethyl, and the like.

"Alkylamino" and "dialkylamino" mean one or two alkyl moieties attached through a nitrogen bridge (*i.e.*, -NHalkyl or –N(alkyl)(alkyl)) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

"Hydroxyalkyl" means an alkyl substituted with at least one hydroxyl group.

"Mono- or di(cycloalkyl)methyl" represents a methyl group substituted with one or two cycloalkyl groups, such as cyclopropylmethyl, dicyclopropylmethyl, and the like.

"Alkylcarbonylalkyl" represents an alkyl substituted with a -C(=O)alkyl group.

"Alkylcarbonyloxyalkyl" represents an alkyl substituted with a -C(=O)Oalkyl group or a -OC(=O)alkyl group.

"Alkoxyalkyl" represents an alkyl substituted with a -O-alkyl group.

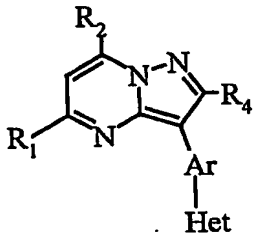
"Alkylthioalkyl" represents an alkyl substituted with a -S-alkyl group.

"Mono- or di(alkyl)amino represents an amino substituted with one alkyl or with two alkyls, respectively.

"Mono- or di(alkyl)aminoalkyl" represents a alkyl substituted with a mono- or di(alkyl)amino.

"Alkylsulfonyl and alkylsulfinyl" represent an alkyl substituted with a sulfonyl (-S(=O)$_2$-) or sulfinyl (-S(=O)-), respectively.

Embodiments of this invention presented herein are for purposes of example and not for purposes of limitation. In a first embodiment of the invention, R_3 is null and Y is =(CR$_4$ in ll ing s u u (and in a u di n Y is (C= in ll ing s u u (:



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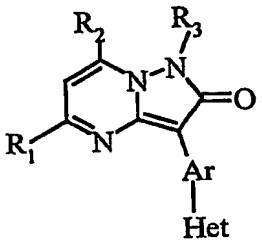

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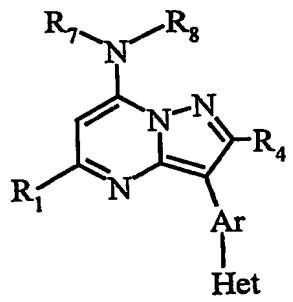
Fu di n s is inv n i n in Y is =(CR$_4$ av s u u (V n R_2 is NR_7R_8 and s u u (V n R_2 is – R_{10}



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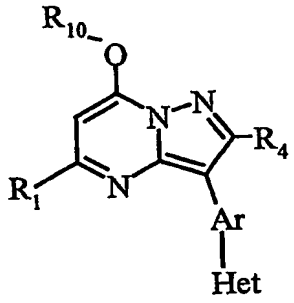

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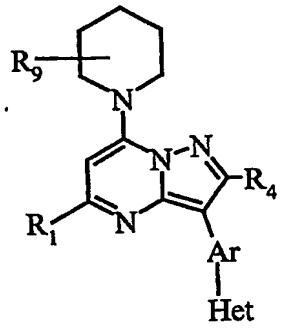
n u di n s is inv n i n in Y is =(CR$_4$ R_2 is NR_7R_8 in R_7 and R_8 g i ni g n i a a a d a l ing li i d (u n li i d si ing a s i an su s i u d 2 3 R_9 in ll ing s u u s (V V :



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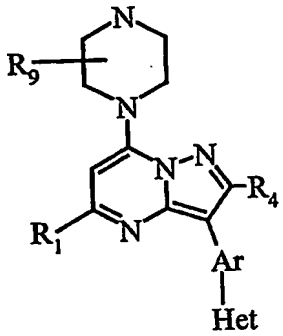

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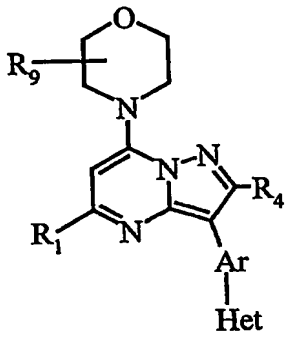
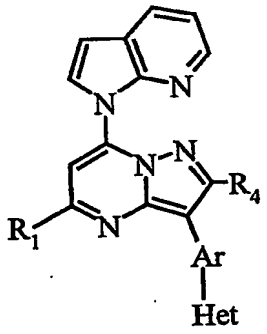


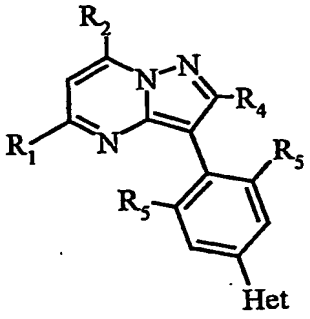
(VIII)

In further embodiments of this invention wherein Y is =C(CR_4 -, R_2 is -NR_7R_8 wherein R_7 and R_8, together with the nitrogen to which they are attached, form a bicyclic heterocycle ring in the following structure (IX :



(IX

In further embodiments of this invention, Ar is phenyl substituted with 2 R_5 in the following structure (X , and Het is pyridyl substituted with R_6 in the following structure (XI .



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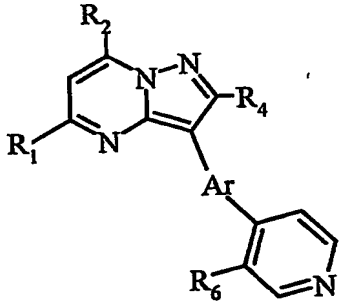
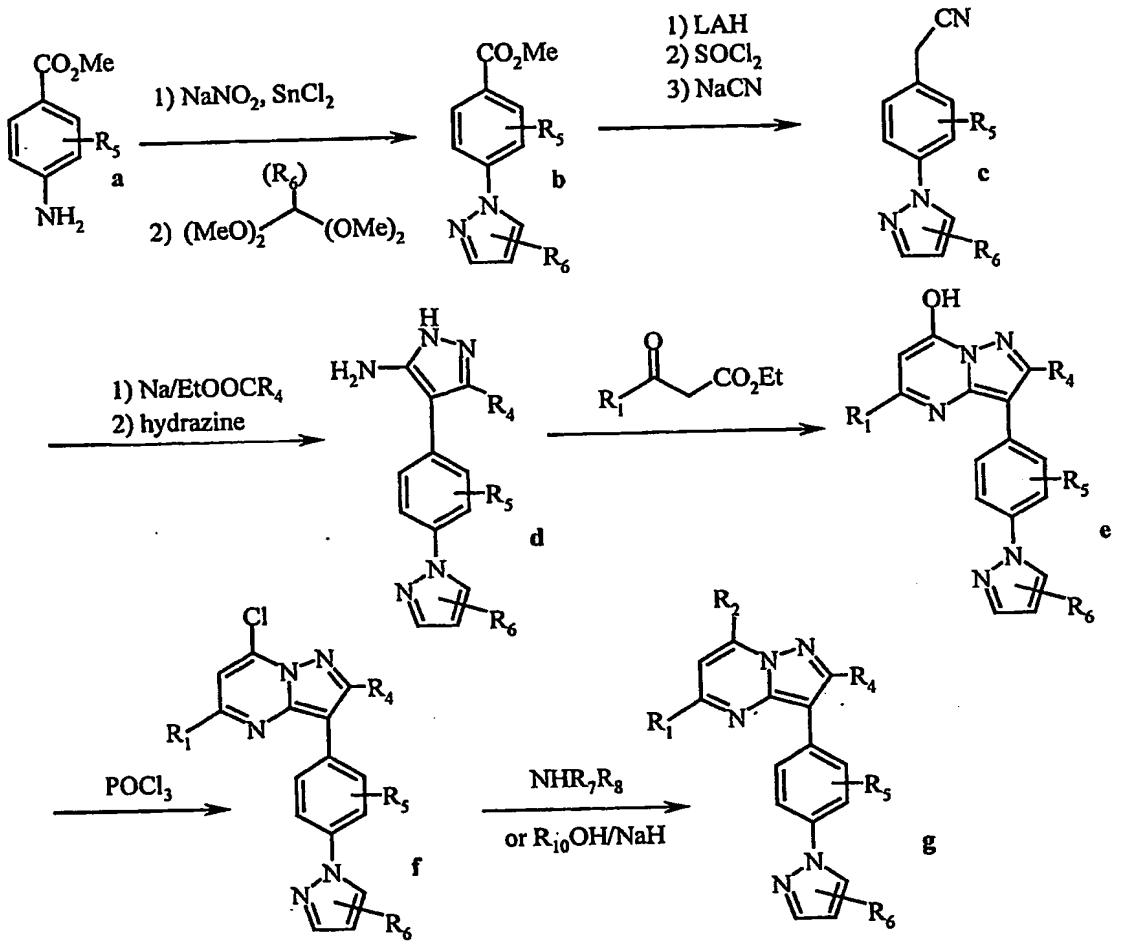


(XI

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

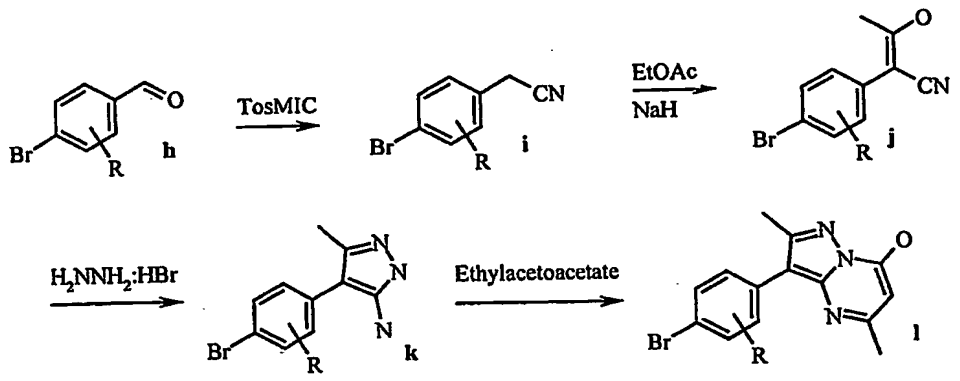
In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples. For example, the synthesis of structure (I) may generally proceed according to the following Reaction Scheme 1.

Reaction Scheme 1



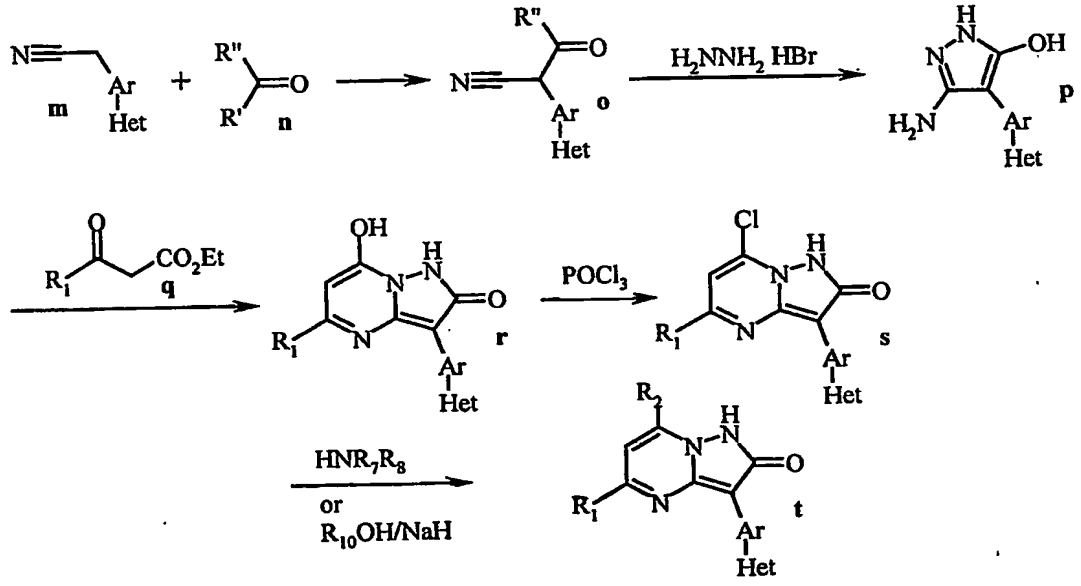
The amino functionality of 4-aminobenzoate **a** may be condensed with a(n) (optionally) substituted malonaldehyde to give the corresponding 4-pyrazol-1-yl benzoate **b**. After reaction with LAH, $SOCl_2$, and NaCN and conversion to the pyrazolophenylacetonitrile compound **c**, reaction with Na/ethyl carboxylic acid ester and hydrazine yields the bis-pyrazole **d**. Reaction with the appropriately substituted □-keto ester gives pyrazolopyrimidine **e** which reacts with $POCl_3$ to give the chloride **f**. Reaction of the chloride **f** with amine or alcohol gives compound **g**.

Reaction Scheme 2



Synthetic routes available to the pyrazolopyrimidine core of the invention abound. In Reaction Scheme 2, the optionally substituted halobenzaldehyde **h** reacts with tosylmethyl isocyanide (TosMIC) to form the phenylacetonitrile **i**. Reaction of **i** with NaH and EtOAc gives the 3-hydroxy but-2-enenitrile **j** which undergoes ring closure in reaction with hydrazine HBr to give the 3-amino 2-phenyl pyrazole **k**. Addition of the □-keto ester gives the pyrazolo[1,5-a]pyrimidin-7-ol **l**. Substitution of the distal bromine with Het gives the invention.

Reaction Scheme 3



Reaction of substituted acetonitrile **m** with ketone **n**, where R' is a good leaving group such as alkoxy, cyano, or halo, and where R" is a group such as hydroxy or alkoxy, gives cyanoketone **o** which reacts with hydrazine to give substituted pyrazole **p**. Reaction of **p** with □-keto ester **q** gives pyrazolopyrimidine **r**.

Reaction with $POCl_3$ gives the chloride **s**, and reaction with amine or alcohol gives compound **t**.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse 1*:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (*e.g.*, [^{125}I]tyrosine-CFR) to its receptor (*e.g.*, receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC_{50} as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation:

$$K_i = \frac{IC_{50}}{1 + L/K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)).

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM. In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1μM, and more preferably less than 0.25 μM (*i.e.*, 250 nM). As set forth in greater detail below, the K_i values may be assayed by the methods set forth in Example 13.

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably,

the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets,

and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

In another embodiment, the present invention permits the diagnostic visualization of specific sites within the body by the use of radioactive or non-radioactive pharmaceutical agents Use of a compound of the present invention may provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. Radioactive pharmaceuticals are employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and single photon emission computerized tomography (SPECT.) For such applications, radioisotopes are incorporated of such elements as iodine (I) including ^{123}I (PET), ^{125}I (SPECT), and ^{131}I, technetium (Tc) including ^{99}Tc (PET), phosphorus (P) including ^{31}P and ^{32}P, chromium (Cr) including ^{51}Cr, carbon (C) including ^{11}C, fluorine (F) including ^{18}F, thallium (Tl) including ^{201}Tl, and like emitters of positron and ionizing radiation. Non-radioactive pharmaceuticals are employed in magnetic resonance imaging (MRI), fluoroscopy, and ultrasound. For such applications, isotopes are incorporated of such elements as gadolinium (Gd) including ^{153}Gd, iron (Fe), barium (Ba), manganese (Mn), and thallium (Tl). Such entities are also useful for identifying the presence of particular target sites in a mixture and for labeling molecules in a mixture.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 4. Example 5 presents a method for determining the receptor binding affinity, and Example 6 discloses an assay for screening compounds of this invention for CRF-stimulated adenylate cyclase activity.

Analytical HPLC-MS (LC-MS)

HP 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: YMC ODS AQ, S-5, 5μ, 2.0 x50 mm cartridge;

HPLC gradients: 1.5 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute.

Prep. HPLC-MS

Gilson HPLC-MS equipped with Gilson 215 auto-sampler/fraction collector, an UV detector and a ThermoFinnigan AQA Single QUAD Mass detector (electrospray);

HPLC column: BHK ODS-O/B, 5 μ, 30x75 mm

HPLC gradients: 35 mL/minute, 10 % acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes.

Abbreviations:

AA: Acetyl acetate

LAH: Lithium aluminum hydride

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

EAA: Ethyl acetoacetate

LC-MS: liquid chromatography-mass spectroscopy

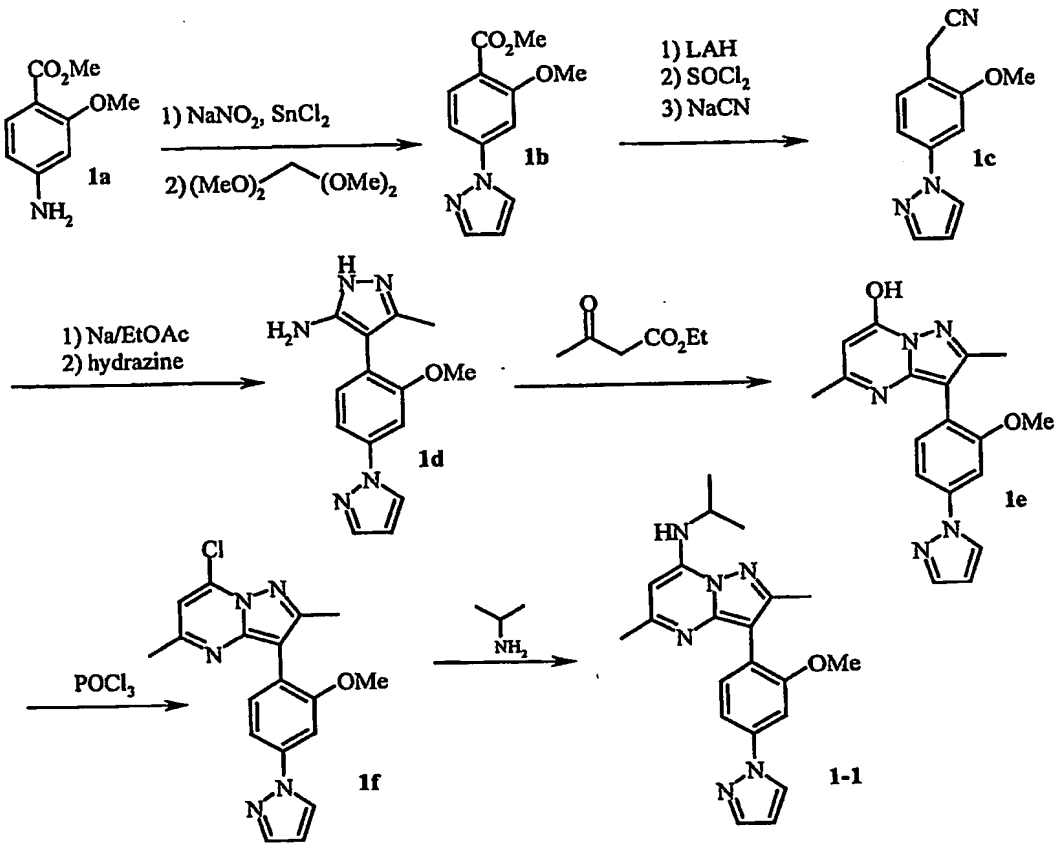
$NaBH(OAc)_3$: Sodium Triacetoxyborohydride

Pd-C: Palladium (10 %) on Carbon

TFA: Trifluoroacetic acid

Tosmic: Tosylmethyl isocyanide

EXAMPLE 1



Step 1A:

To a cooled suspension of methyl 4-amino-2-methoxybenzoate (6.82 g, 37.7 mmol) in 6N HCl (aqueous) was added a solution of sodium nitrite (2.60 g, 37.7 mmol) dropwise. After stirring at 0 °C for 20 min, stannous chloride dihydrate (24.7 g, 109.3 mmol) was added portionwise. The resulting suspension was stirred at 0 °C for 1.5 h prior to filtration. The collected solid was suspended in EtOH to which malonaldehyde bis(dimethyl acetal) (7.5 mL, 45.7 mmol) was added, and this reaction mixture was subjected to reflux overnight. After evaporation of EtOH, the residue was extracted between EtOAc and water, and the organic phase was dried and evaporated to dryness. The residue was passed through a silica gel plug with 25% EtOAc/hexane to give compound **1b** (7.43 g) as a mixture of methyl and ethyl benzoates.

Step 1B:

To a solution of **1b** (10.6 g) in dry diethyl ether (200 mL) was added LAH powder (1.74 g) slowly at 0 °C. After stirring for 45 min at 0 °C the reaction mixture was decanted onto ice-water, and the aqueous phase was acidified to pH 4.0. After isolation, the alcohol was refluxed with thionyl chloride (10 mL) in DCM for 2.5 h, decanted onto ice-water, and extracted with DCM. The crude benzyl chloride was heated with NaCN (3.65 g, 74.4 mmol) in DMSO (100 mL) at 80 °C for 45 min. After removal of DMSO, compound **1c** (5.98 g) obtained after chromatographic purification.

Step 1C:

To a solution of **1c** (5.98 g, 28.1 mmol) in EtOAc (150 mL) was added metallic sodium (1.0 g, 43.5 mmol) portionwise, and the mixture was refluxed overnight. The resulting suspension was decanted onto ice-water and acidified to pH 4.0. The organic phase was dried, evaporated to dryness, mixed with hydrazine monohydrobromide (15.3 g, 135.4 mmol,) and refluxed for 5 h in EtOH/H_2O (6:1.) The organic phase was dried and evaporated to dryness to yield compound **1d** (10.4 g.)

Step 1D:

A mixture of **1d** (7.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in AcOH (100 mL) for 3 h. After evaporation of AcOH and precipitation in diethyl ether, compound **1e** (10.4 g) obtained after filtration.

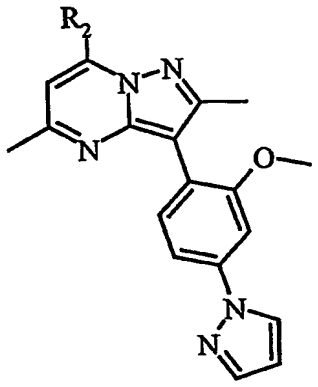
Step 1E:

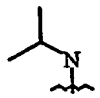
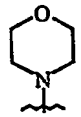
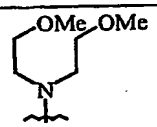
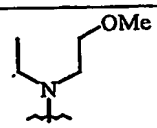
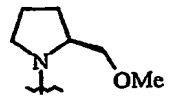
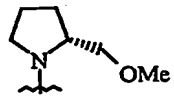
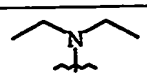
To a suspension of **1e** (2.1 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol,) and the mixture was refluxed for 5h, decanted to ice-water, and extracted with EtOAc to yield compound **1f** (1.88 g) after chromatographic purification.

Step 1F:

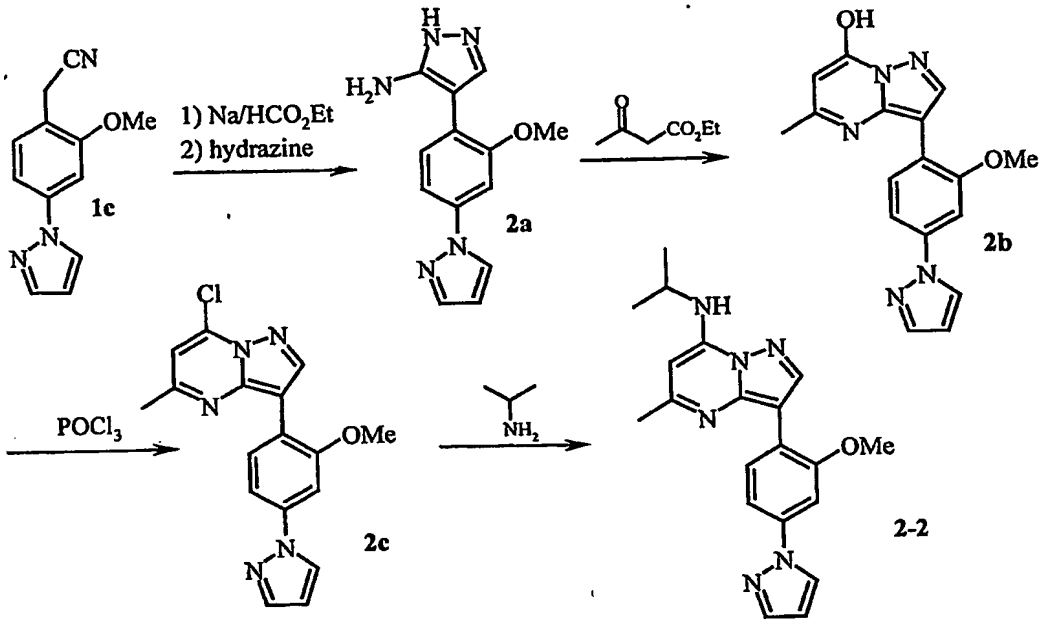
Displacement of the chlorine with isopropylamine followed suspension of **1f** (30 mg) and excess amine in acetonitrile (0.8 mL), heating to 160 °C with microwave for 16 min, and purification with the Sciex2 preparative LC-MS system to

give compound **1-1** (13.5 mg.) Depending on the reacting amine, reaction of **1f** with amine gave the compounds listed in the following table.



	R_2	MW	MS	RT
1-1		376.46	376	1.497
1-2		404.47	404	1.573
1-3		450.54	450	1.493
1-4		420.52	420	1.528
1-5		376.46	376	1.505
1-6		432.52	432	1.526
1-7		432.52	432	1.521
1-8		362.44	362	1.567
1-9		390.49	390	1.518

EXAMPLE 2



Step 2A:

In order to introduce hydrogen at position R_4 of the invention, the synthetic scheme of Example 1 was modified at Step 1C to give the synthetic scheme of Example 2. To a solution of **1c** (1.0 g) in HCO_2Et (20 mL) was added metallic sodium (0.13 g) portionwise, and the mixture was refluxed for 1.5 h. The resulting suspension was decanted onto ice-water and acidified to pH 4.0. The organic phase was dried, evaporated to dryness, mixed with hydrazine monohydrobromide (1.58 g) and refluxed for 1 h in EtOH/H_2O (6:1.) After evaporation of EtOH, the mixture was extracted between EtOAc and NaOH (aq.) The organic phase was dried and evaporated to dryness to yield compound **2a** (1.20 g.)

Step 2B:

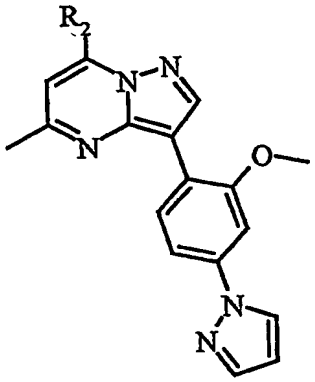
A mixture of **2a** (1.2 g) was refluxed with ethyl acetoacetate (1.0 mL) in AcOH (30 mL) for 2 h. After evaporation of AcOH and precipitation in diethyl ether, compound **2b** (1.0 g) obtained after filtration.

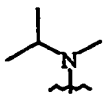
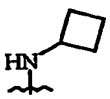
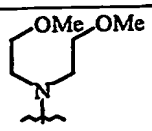
Step 2C:

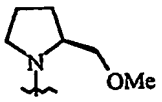
To a suspension of **2b** (1.0 g) in acetonitrile (30 mL) was added $POCl_3$ (2.0 mL,) and the mixture was refluxed overnight, decanted to ice-water, and extracted with EtOAc to yield compound **2c** (0.92 g) after chromatographic purification.

Step 2D:

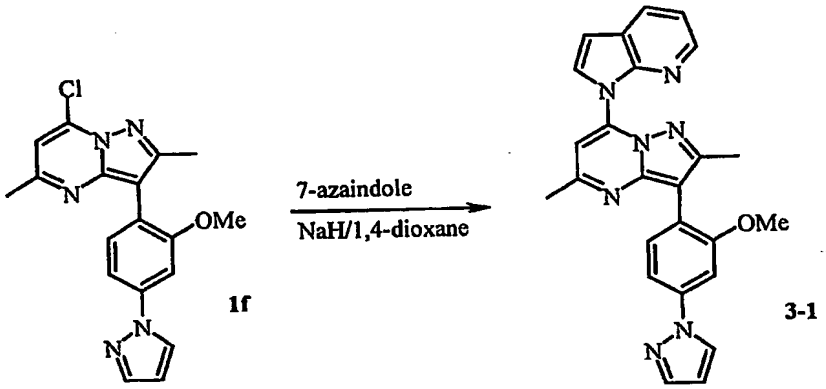
Displacement of the chlorine with isopropylamine followed suspension of **2c** (30 mg) and excess amine in acetonitrile (0.8 mL), heating to 160 °C with microwave for 16 min, and purification with the Sciex2 preparative LC-MS system to yield compound **2-2** (14.8 mg.) Depending on the reacting amine, reaction of **2c** with amine gave the compounds listed in the following table.



	R_2	MW	MS	RT
2-1		376.46	376	1.577
2-2		362.44	362	1.512
2-3		362.44	362	1.650
2-4		374.45	374	1.611
2-5		436.51	436	1.451

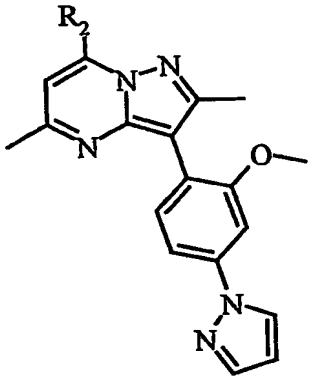
2-6		418.50	418	1.564

EXAMPLE 3

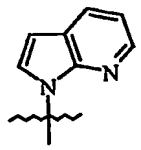


Step 3A:

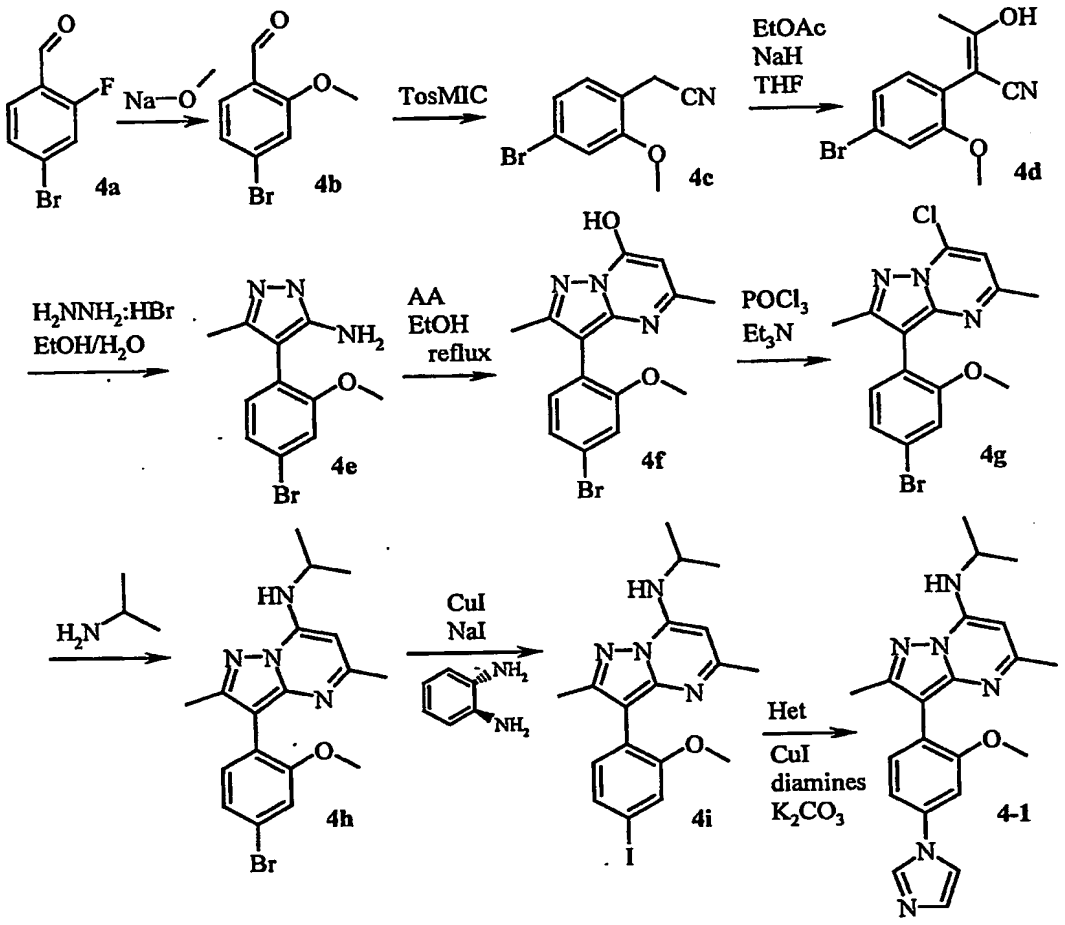
To a solution of 7-azainole (24 mg) in dry 1,4-dioxane was added NaH (12 mg) with stirring for 15 min. Compound **1f** (35 mg) was added with stirring overnight. Preparative LC-MS purification gave compound **3-1** (6.1 mg.) Depending on the reacting amine, reaction of **1f** with amine gave the compound(s) listed in the following table.



	R_2	MW	MS	RT

3-1		435.49	435	1.601

EXAMPLE 4



5 Step 4A:

Compound 4a (40 g, Aldrich,) was dissolved in 200 mL THF. Sodium methoxide solution (48 mL, 25% in MeOH) was added dropwise, and the reaction mixture was stirred at room temperature for 6 hr. Following quenching with 150 mL water, the mixture was neutralized with 4N HCl and extracted with DCM. The

organic layer was dried under sodium sulfate, concentrated, and purified by silica gel chromatography to give compound **4b** (17.7 g.)

Step 4B:

A suspension of potassium *t*-butyloxide (7.3 g) in DME (40 mL) was chilled to –50 °C under nitrogen. Tosmic (9.1 g) in DME (40 mL) was added dropwise with maintenance of temperature. To the reaction mixture was introduced compound **4b** (10 g) with stirring for 30 min. MeOH (100 mL) was added, and the reaction mixture was refluxed for 30 min. After removal of most of the DME and MeOH, the residue was resuspended in water (100 mL) and ethyl acetate (100 mL) and neutralized with acetic acid. The organic layer was washed with brine, dried under sodium sulfate, concentrated, and purified with silica gel chromatography to give compound **4c** (7.0 g.)

Step 4C:

Under nitrogen, to compound **4c** (6.25 g) dissolved in THF (80 mL) was added NaH (2.3 g, 60% in oil) and ethyl acetate (1.5 mL.) The mixture was gently heated with a handheld heat gun until small bubbles evolved from the mixture. Ethyl acetate was added to keep the reflux. The reaction was kept at room temperature for one hour, quenched with water (100 mL,) and extracted with diethyl ether (100 mL.) The aqueous solution was neutralized with 4N HCl and extracted twice with ethyl acetate (100 mL aliquots.) The organic layer was dried over sodium sulfate and concentrated to give compound **4d** (6.5 g.)

Step 4D:

Compound **4d** (12.1 g) and hydrazine:HBr (5.61 g) were dissolved in EtOH:H_2O (100 mL, 9:1 mixture,) and the mixture was refluxed for 2 hr. After concentration, the mixture was partitioned between ethyl acetate (200 mL) and saturated sodium bicarbonate (150 mL.) The organic layer was dried under sodium sulfate and concentrated to give compound **4e** (12.2 g.)

Step 4E:

Compound **4e** (12.2 g) and acetyl acetate (9.06 g) were mixed with ethanol (50 mL) and the mixture was refluxed overnight. Upon cooling, crystals

formed and were harvested. The filtrate was further treated with diethyl ether to afford compound **4f** (10.76 g.)

Step 4F:

Compound **4f** (2.0 g) was dissolved in $POCl_3$ (1.34 mL, 14.44 mmol) and Et_3N (1.6 mL) to which dioxane (10 mL) was added, and the mixture was refluxed 2 hr. The reaction mixture was poured over ice and sodium carbonate was added to adjust to pH 7. Extraction with EtOAc, drying over MgSO4, filtration and evaporation were followed by chromatography to give compound **4g** (2.0 g.)

Step 4G:

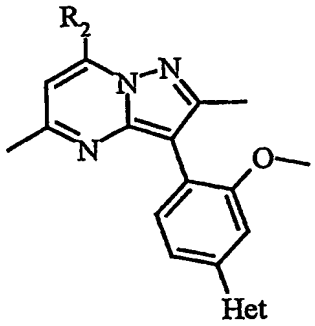
To compound **4g** (1.0 g) in ethanol (10 mL) was added isopropylamine (2.0 eq.) The reaction mixture was heated overnight in a pressure vessel. Removal of ethanol and column chromatography yielded compound **4h** (0.95 g.)

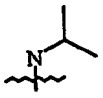
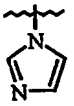
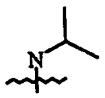
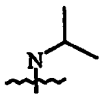
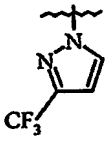
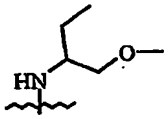
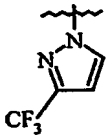
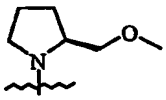
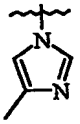
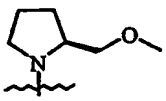
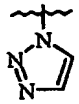
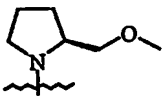
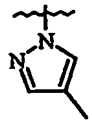
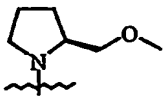
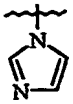
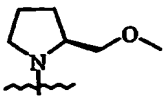
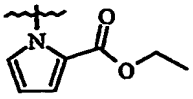
Step 4H:

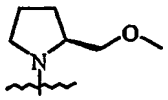
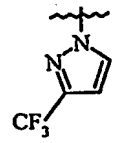
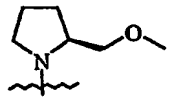
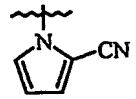
To compound **4h** (0.8 g) in dioxane (20 mL) was added CuI (0.03 g,) NaI (0.63 g,) and *trans*-1,2-diaminocyclohexane (0.0036 mL), and this mixture was heated overnight at 110 °C. The reaction mixture was filtered, the dioxane was removed, and the residue was dissolved in EtOAc and washed with brine. Filtration through silica gel yielded compound **4i** (0.81 g.)

Step 4I:

To compound **4i** (40 mg) in dioxane (2 mL) was added imidazole (1.5 eq), CuI (26.8 mg,) K_2CO_3 (53.2 mg,) *trans*-1,2-diaminocyclohexane (0.0015 mL,) and N,N-dimethylenediamine (0.0014 mL,) and this reaction mixture was heated to 110 °C overnight. The reaction mixture was filtered and purified via preparative HPLC to give compound **4-1** (8.3 mg.) Depending on the reagents employed in this synthetic scheme for the R_2 and Het positions of the invention, the compounds in the following table were obtained.



	R_2		MW	MS	RT
4-1			376.46	377	1.671
4-2			390.49	391	1.554
4-3			444.46	445	2.318
4-4			488.51	489	1.478
4-5			446.55	447	3.830
4-6			433.51	434	5.640
4-7			446.55	447	5.900
4-8			432.52	433	3.730
4-9			503.60	504	5.630

4-10			500.52	501	5.650
4-11			456.55	457	5.260

EXAMPLE 5

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10μg cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 ml assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 ml of [^{125}I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hours at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters. Following three washes, the filters are dried and radioactivity (Auger electrons from ^{125}I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XL*fit* (ID Business Solutions Ltd).

EXAMPLE 6

CRF-STIMULATED ADENYLATE CYCLASE ACTIVITY

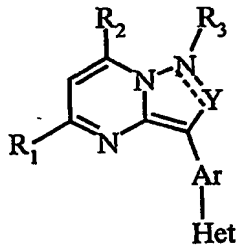
The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as generally described by Battaglia et al. (*Synapse 1*:572, 1987) with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final volume of 0.1 ml: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 96-well plates and incubated for 30 min at 37 °C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, cAMP in the samples is measured using standard commercially available kits, such as cAMP-Screen™ from Applied Biosystems. For the functional assessment of the compounds, cells and a single concentration of CRF or related peptides causing 50% stimulation of cAMP production are incubated along with various concentrations of competing compounds for 30 min at 37°C, and cAMP determined as described above.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the following structure:



or a stereoisomer, prodrug and pharmaceutically acceptable salt thereof,

wherein:

"---" represents the second bond of an optional double bond;

R_1 is hydrogen, alkyl, substituted alkyl, $-NH_2$, or halogen;

R_2 is $-NR_7R_8$ or $-OR_{10}$;

R_3 is null, hydrogen, or alkyl;

Y is $=(CR_4)-$ or $-(C=O)-$;

R_4 is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl optionally substituted with 1 or 2 R_5;

R_5 at each occurrence is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfinyl, or alkylsulfonyl;

Het is heteroaryl optionally substituted with 1 or 2 R_6;

R_6 at each occurrence is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, or hydroxy;

R_7 is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, or alkoxyalkyl;

R_8 is alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, alkoxyalkyl, substituted alkoxyalkyl, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, arylalkyl, or substituted arylalkyl; or

R_7 and R_8, together with the nitrogen atom to which they are attached, form a heterocycle which is optionally substituted by 1, 2, or 3 R_9;

R_9 at each occurrence is hydrogen, hydroxy, alkylsulfonyl, alkylsulfinyl, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, alkoxyalkyl, or substituted alkoxyalkyl; and

R_{10} is alkyl, substituted alkyl, heteroarylalkyl, substituted heteroarylalkyl, aryloxyalkyl, or substituted aryloxyalkyl.

2. The compound of claim 1 wherein R_1 is hydrogen, alkyl, or substituted alkyl.

3. The compound of claim 1 wherein R_2 is $-NR_7R_8$.

4. The compound of claim 3 wherein R_7 and R_8 together with the nitrogen atom to which they are attached from a heterocycle substituted by 1 R_9.

5. The compound of claim 4 where R_9 is hydroxy, alkylsulfonyl, alkylsulfinyl, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, alkoxyalkyl, or substituted alkoxyalkyl.

6. The compound of claim 1 wherein R_3 is null.

7. The compound of claim 6 wherein Y is $=(CR_4)-$.

8. The compound of claim 7 wherein R_4 is hydrogen, alkyl, or substituted alkyl.

9. The compound of claim 1 wherein R_3 is hydrogen or alkyl.

10. The compound of claim 9 wherein Y is $-(C=O)-$.

11. The compound of claim 1 wherein Ar is substituted by 1 R_5.

12. The compound of claim 11 wherein R_5 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen.

13. The compound of claim 1 wherein Het is substituted by 1 R_6.

14. The compound of claim 13 wherein R_6 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen.

15. A composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.

16. A method for treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal comprising administering to the animal an effective amount of the pharmaceutical composition of claim 15.

17. The method of claim 16 wherein the disorder is stroke.

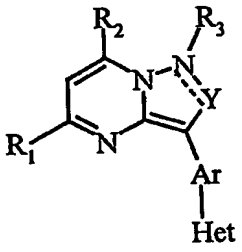
18. The method of claim 16 wherein the disorder is depression.

19. The method of claim 16 wherein the disorder is obsessive-compulsive disorder.

20. The method of claim 16 wherein the disorder is irritable bowel syndrome.

ABSTRACT OF THE DISCLOSURE

CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals, such as stroke. The CRF receptor antagonists of this invention have the following structure:



including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R_1, R_2, R_3, Y, Ar, and Het are as defined herein. Compositions containing a CRF receptor antagonist in combination with a pharmaceutically acceptable carrier are also disclosed, as well as methods for use of the same.

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